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## USSR WORK PERTAINING TO THE ACTION OF DRUGS ON NERVE REGULATION

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In searching for new and active drugs, one must try to bring the constitution of synthetic drugs as close as possible to that of natural chemical substances which participate in the biochemical processes of the organism. The constitution of natural biochemically active substances, as well as the manner in which they act, can be clarified by investigating biochemical processes and the enzyme systems which guide these processes. This type of investigation is very difficult as far as synthesis of drugs acting on the central nervous system are concerned. It is less difficult when the final aim is development of substances that act selectively on peripheral conducting nerve paths at the places where impulses are transmitted.

Knowing the constitution of acetylcholine and adrenalin, we are able to synthesize substances which exhibit an analogous action. Other (synthetic) esters of choline besides acetylcholine react similarly to acetylcholine with cholinoreactive systems, i.e., those dynamic biochemical tissue systems with which acetylcholine itself normally reacts. The acetylcholine antagonists known as cholinolytic agents are of great therapeutic value. By blocking the transmission of central impulses, they are able to produce functional rest and in this manner contribute to restoration of the normal state.

If the structure of cholinolytic substances is appropriately modified, the action of therapeutic doses of these substances can be restricted to the cholinoreactive systems of definite elements of the organism, e.g., to the vegetative ganglia only or the skeletal muscles only. USSR pharmacologists and chemists have created a number of drugs having a ganglionic or curare-like action. These drugs are being successfully used both in experiments and in the clinic when the necessary indications exist.

Substances which have a relatively broad selective action and, in addition, possess other useful pharmacological characteristics are of the greatest value for therapy. A substance of this type, diphacyl or spasmolytine, was proposed abroad under the name of trasentine and recommended for use as an atropine-like spasmolytic. The pharmacological evaluation of diphacyl abroad was based exclusively on experiments with isolated organs.

Investigation in the USSR, from the standpoint of Pavlov's concept to the effect that the organism reacts as a whole, disclosed that diphacyl has additional pharmacological properties of value. Thus, T. N. Tomilina, our collaborator, showed that in addition to exerting a weak action of the atropine type, diphacyl blocks ganglia and also has a specific effect on the central nervous system. It furthermore acts as a local anesthetic.

It is probable that the beneficial effect of diphacyl on gastrointestinal ulcers is due to its action on the central nervous system.

The method of conditioned reflexes is extremely useful for evaluating drugs of this type. Although investigations of this kind have only been started recently, they have already yielded interesting results. For instance, S. S. Krylov established that diphacyl has an effect on conditioned salivation reflexes of dogs in doses which do not yet produce any peripheral action.

Lately, good results have been achieved in the synthesis of analgesics. Data on promedol, a very valuable analgesic synthesized by I. N. Nazarov, Corresponding Member of the Academy of Medical Science USSR, have been published recently. Phenadon belongs to the same series of new synthetic analgesics.

The effect of phenadon on conditioned reflexes was investigated in detail by M. M. Lenkevich. He established that this drug acts on the higher nervous activity in doses which are 100 times smaller than those which exert a therapeutic effect.

Contrary to the opinion widely held by foreign investigators in regard to the action of drugs of the morphine class, the analgesic action of phenadon is mainly of the cortical rather than of the stem type. This is explained by the fact that the conditioned vascular reflexes of human beings, which arise as a result of an unconditioned pain irritation, are affected by phenadon earlier than the unconditioned reflexes. The strengthening of inhibition processes under the influence of therapeutic doses of phenadon, which has been proven by Lenkovich, may be of practical interest.

The selective action of pharmacologically active substances of plant origin is explained by the resemblance of their chemical constitution to that of substances which participate in biochemical processes taking place in animal tissue. The fact that caffeine is a purine derivative may be cited as an example proving the truth of this statement.

In synthesizing dibasol, use was made of the principle just mentioned. Dibasol has a structural skeleton corresponding to that of papaverine, i.e., of an alkaloid which has a vasodilative action. This skeleton has been modified in such a manner that the constitution of dibasol approaches that of substances which play an important part in animal metabolism. The result is a drug which has the vasodilative activity of papaverine but also exerts a specific stimulating effect on the central nervous system, particularly under pathological conditions.

Pavlov's method of experimental therapy with the use of biological models of human disease conditions is being applied to an increasing extent by USSR pharmacologists for the study of the action of drugs on nerve regulation. Work

of this type led to the conclusion that drugs which affect nerve regulation act more strongly under pathological conditions, i.e., when normal regulation has been disturbed. To evaluate the effects of drugs on nerve regulation under pathological conditions, it is best to study these drugs against the background of reflex reactions that influence processes having a bearing on trophism. When a strong mechanical or chemical trauma is applied to the pyloroduodenal region of experimental animals, the animals develop intestinal ulcers by reflex action (I. S. Zavodskaya). Testing on this experimental model of drugs which have an effect on various links of the pathological reflex arc showed that interruption of this arc can prevent formtion of the experimentally produced ulcer. Breaking of the reflex arc can be achieved by means of luminal, which acts centrally; of tetraethylammonium, which blocks ganglia; or of esters of the diphacyl type, which act on many links of the reflex arc.

In the investigation of actions of this type on the reflex arc, the study of the effect of pharmacologically active compounds on the sensitive nerve endings (receptors) is of particular importance. On the basis of clinical data and theoretical considerations, one must conclude that not only substances which irritate receptors but also substances which lower the susceptibility of receptors must form the subject of pharmacological investigation. USSR pathologists and clinicists deserve credit for introducing the novocain block into general medical practice. Although the novocain block is often very effective from the physiological standpoint, novocain is far from being perfect as far as its pharmacological action is concerned.

When we apply an anesthetic for the blocking of a conducting nerve path or for the isolation of a reflexogenic zone, we try to break the reflex arc. Under the circumstances, it is of importance that effects due to resorption (i.e., central and ganglionic effects) be added to the local action of the drug. The duration of the blocking effect is also of great importance. In all these respects, some of the newer drugs, particularly diphacyl, are much superior to novocain.

For that reason, we proposed that diphacyl be used to block the sympathetic nerve chain in endoarterites and for the regional blocking of skin areas in cases of ischialgia, radiculatis, and gastrointestinal ulcers. Diphacyl is very effective in eliminating the pain syndrome which accompanies these conditions.

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